EMULSIONS AND MICROEMULSIONS

Gillian M. Eccleston
University of Strathclyde, Glasgow, United Kingdom

EMULSIONS

An emulsion is a heterogeneous preparation composed of two immiscible liquids (by convention described as oil and water), one of which is dispersed as fine droplets uniformly throughout the other. Emulsions are thermodynamically unstable and revert back to separate oil and water phases by fusion or coalescence of droplets unless kinetically stabilized by a third component, the emulsifying agent. The phase present as small droplets is called the disperse, dispersed, or internal phase and the supporting liquid is known as the continuous or external phase. Droplet diameters vary enormously, but in pharmaceutical emulsions they are typically polydispersed with diameters ranging from approximately 0.1 to 50 μm. Emulsions are conveniently classified as oil-in-water (o/w) or water-in-oil (w/o), depending on whether the continuous phase is aqueous or oily. Fig. 1a shows a photomicrograph of a simple o/w system. Practical pharmaceutical emulsions, however, are rarely simple two-phase oil and water preparations; many are multicomponent systems containing additional solid or liquid crystalline (e.g. lamellar) phases (Fig. 1b). Multiple emulsions, which are prepared from oil and water by the reemulsification of an existing emulsion so as to provide two dispersed phases, are also of pharmaceutical interest. Multiple emulsions of the oil-in-water-in-oil (o/w/o) type are w/o emulsions in which the water globules themselves contain dispersed oil globules; conversely, water-in-oil-in-water (w/o/w) emulsions are those where the internal and external aqueous phases are separated by the oil (Fig. 1c). These more complex emulsions are covered by the broader International Union of Pure and Applied Chemistry (IUPAC) definition of emulsions, which extends the classical definition to include "liquid droplets and/or liquid crystals dispersed in a liquid" (1).

Emulsions are formulated for virtually all the major routes of administration, and there are a number of dermatological, oral and, parenteral preparations available commercially. The internal phase may contain water-soluble drugs, preservatives, and flavoring agents whilst the oil phase may itself be therapeutically active or may act as a carrier for an oil-soluble drug. Such preparations provide an effective approach to many of the problems in drug delivery, often showing distinct advantages over other dosage forms by way of improved bioavailability and/or reduced side effects. However, despite such advantages, emulsions are not used as extensively as other oral or parenteral dosage forms due to the fundamental problems of emulsion instability that result in unpredictable drug release profiles and possible toxicity. The full potential of emulsions will not be realized until stable systems are developed with predictable in vitro and in vivo release patterns. Much of the emulsion research over the past decade is based on attempts to understand the relationships between emulsion stability, physicochemical properties, and biological fate. Multiple emulsions are even more difficult to stabilize, and characterize and although there is an increasing interest in their potential applications for drug delivery, at present there are no commercial preparations available (2).

PHARMACEUTICAL APPLICATIONS

The current and potential pharmaceutical applications of emulsions have been the subject of a number of general reviews (3–6). Traditionally the term "emulsion" is restricted to mobile emulsions for internal use; emulsions for external use are described by their pharmaceutical types as liniments, lotions, and creams. This tends to conceal the fact that by far the largest group of emulsions currently used in pharmacy and medicine are dermatological emulsions for external use (7, 8). Both oil-in-water and water-in-oil emulsions are extensively used for their therapeutic properties and/or as vehicles to deliver drugs and cosmetic agents to the skin. The emulsion facilitates drug permeation into and through the skin by its occlusive effects and/or by the incorporation of penetration-enhancing components. Particular attention is paid to patient acceptance of such formulations, which range in consistency from mobile liniments and lotions to semisolid ointments and creams. In the past, the development of dermatological emulsions was essentially empirical with only a limited understanding of the

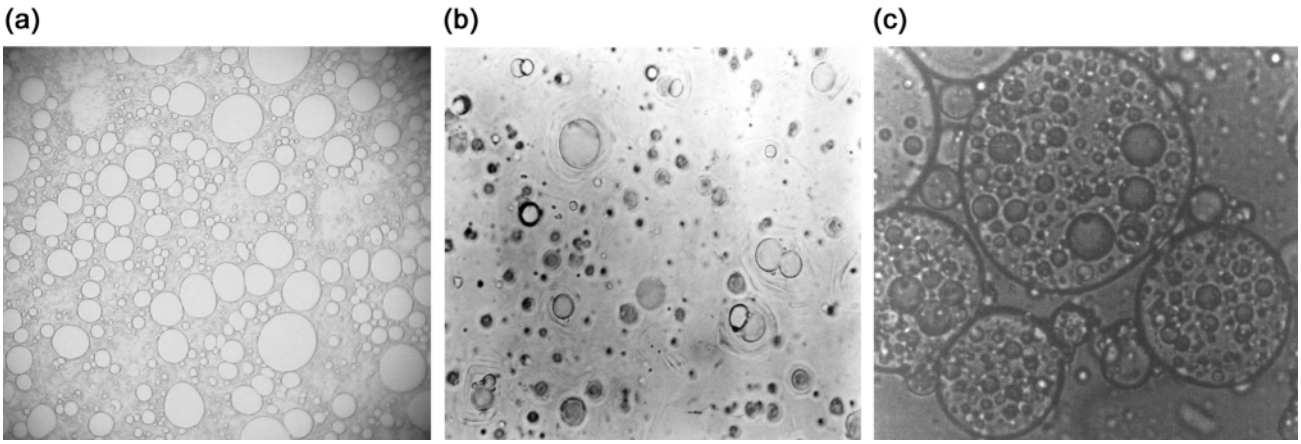

Fig. 1 Photomicrographs of typical emulsions. (a) A liquid paraffin-in-water emulsion stabilized by 1.89% Span 40 and 1.62% Tween 80. The polydispersity of the oil droplets before homogenization is clearly seen. (b) A liquid paraffin–water cream stabilized by a cationic emulsifying wax. Note the lamellar structures surrounding the oil droplets. (c) A multiple w/o/w emulsion. Water droplets can clearly be seen within the larger oil droplets.

underlying principles. Today, although the microstructure of many of these complex formulations is now better understood (9, 10), the mechanisms by which the structure of an emulsion can influence drug bioavailability are far from clear and much of the literature on the role of emulsions in drug release to the skin is contradictory. Confusion arises because the majority of investigations concerning in vitro vehicle effects on drug release are only on bulk formulation. As most emulsions are applied to the skin as a thin film, the drug delivery system is not one of bulk emulsion, but rather a dynamic evaporating system in which phase changes can occur as the preparation is rubbed into the skin and the relative concentrations of volatile ingredients alter. Droplet size appears to influence drug delivery to the skin, with submicron lipid emulsions enhancing the transcutaneous permeation and efficiency of a number of lipophilic drugs (11).

Oral emulsions are almost exclusively of the oil-in-water type. They provide a degree of taste masking as the aqueous external phase effectively isolates the oil from the tongue. Mineral and castor oils have been emulsified in water and administered orally for the local treatment of constipation for many years (cf. Mineral Oil Emulsion USP) as have various nutritional oils from fish liver (generally halibut or cod) or vegetable origin to produce oral liquid food supplements. It has long been established that the use of o/w emulsions as carriers for lipophilic drugs may improve oral bioavailability and efficacy (3–6). For example, griseofulvin formulated as an o/w emulsion has enhanced gastrointestinal absorption when compared with suspensions, tablets, or capsule dosage forms (12). The mechanisms by which emulsions modify and improve absorption processes are complex and not fully understood, although the oil itself influences gastric motility. Fats and oils are solubilized by the bile salts so that the administration of already emulsified oil droplets containing a high concentration of drug may increase the likelihood of further droplet and drug solubilization and transport across the GI tract by the fat absorption pathways.

The type of emulsion used parenterally depends on the route of injection and the intended use (13–15). Oil-in-water emulsions are administered by all the major parenteral routes whereas water-in-oil emulsions are generally reserved for intramuscular or subcutaneous administration where sustained release is required. Drug action is prolonged in such oily emulsions because the drug has to diffuse from the aqueous dispersed phase through the oil-continuous environment to reach the tissue fluids. Water-in-oil emulsions are used to disperse water-soluble immunizing antigens in mineral oil for injection via subcutaneous or intramuscular routes as adjuvant preparations where they prolong and enhance the antigenic stimulus and increase the antibody titer. Oily emulsion formulations also show promise in cancer chemotherapy as vehicles for prolonging drug release after intramuscular or intratumoral injection, and as a means of enhancing the transport of anticancer agents via the lymphatic system (16). Water-in-oil emulsions for sustained release are often difficult to inject because of the high viscosities of the oily continuous phases. Although these problems can be overcome by reemulsification of the primary w/o emulsion to produce a less viscous multiple w/o/w emulsion, a study using

Table 1 Some commercial lipid emulsions for parenteral nutrition

Trade name	Oil phase (%)	Emulsifier (%)	Other components (%)
Intralipid® (Fresenius Kabi)	Soybean (10 and 20)	Egg lecithin (1.2)	Glycerol (2.2), phosphate (15mm/l)
Lipovenos® (Fresenius Kabi)	Soybean (10 and 20)	Egg lecithin (1.2)	Glycerol (2.5)
Liposyn® (Abbott)	Safflower and soybean, 1:1 (10 and 20)	Egg lecithin (1.2)	Glycerol (2.5)
Lipofundin® (Braun)	Cottonseed (15)	Soybean lecithin (0.75)	Sorbitol (5.0), DL-α-Tocopherol
Lipofundin N® (Braun)	Soybean (10 and 20)	Egg lecithin (0.75 and 1.2)	Glycerol (2.5)
Lipofundin MCT/LCT® (Braun)	Soybean and MCT, 1:1 (10 and 20)	Egg lecithin (0.75 and 1.2)	Glycerol (2.5)

5-fluorouracil implied that sustained release was actually less marked with multiple emulsions (17).

Sterile parenteral oil-in-water emulsions have been used extensively for over 40 years for the intravenous administration of fats, carbohydrates, and vitamins to debilitated patients. Several vegetable oil-in-water emulsions are now available commercially with droplet sizes similar to that of chylomicrons (approximately 0.5–2 μm), the natural fat droplets in the blood that transport ingested fats to the lymphatic and circulatory systems (Table 1). More recently, such emulsions have been employed as intravenous carriers for poorly water-soluble lipophilic drugs such as vitamin K (e.g., Sterile Phytonadione Injection U.S.P.) diazepam (e.g., Diemuls®), vitamin A (Vitlipid N®), and profonol (Diprovan®) as alternatives to the traditionally used cosolvent, surfactant solubilized, or pH controlled parenteral solutions. The drug dissolved in the oil phase of the emulsion is unlikely to precipitate and cause pain when diluted by blood on injection, and if susceptible to hydrolysis or oxidation, it will be protected by the nonaqueous environment. Emulsion formulations of diazepam and more recently clarithromycin have been clinically shown to be less painful than solubilized preparations (18, 19) while emulsions containing amphoteracin B are less toxic (20). This emulsion was also shown to be an equally effective, cheaper, and more elegant alternative to a liposomal system. The enormous literature on the potential of lipid emulsions for drug delivery and targeting is discussed in a recent book (21).

Radiopaque emulsions, which have long been used as contrast media in conventional X-ray examinations of body organs, are finding further application with more sophisticated techniques including computed tomography, ultrasound, and nuclear magnetic resonance. Perfluorochemical emulsions are used as artificial blood substitutes. The potential advantages of such systems over donated blood are enormous with the elimination of major donor associated problems such as blood group incompatibilities and blood disease. The first commercial product, Fluosol-DA® (Green Cross Corporation, Osaka, Japan) was licensed several years ago in a number of countries to reduce myocardial ischaemia in patients undergoing angioplasty; however, Fluosol-DA was not a commercial success due to its slow excretion rate and to its marked instability, which meant that it had to be stored in the frozen state. In addition, some patients were sensitive to one of the emulsifiers, pluronic F68®. Currently, a second generation of emulsions is being evaluated to resolve the problems encountered with Fluosol (22) and these are discussed in another chapter of this encyclopedia.

There are only a few studies on the ocular and nasal applications of emulsions. Lipid (submicron) emulsions exhibited a long-lasting antidepressant effect on the intraocular pressure of rabbits after a single application when used as carriers for lipophilic antiglaucoma drugs (23). Medium-chain triglyceride emulsions formulated at pH 8 show potential as controlled release formulations for nasal delivery (24, 25) for they give prolonged drug residence in the nasal cavity (Fig. 2). Enhanced nasal delivery of insulin was observed when insulin was incorporated into the continuous phase of an o/w emulsion, but not when incorporated into the aqueous phase of a w/o emulsion (26).

FORMULATION CONSIDERATIONS

The choice of oil, emulsifier, and emulsion type (o/w, w/o, or multiple) is limited by its ultimate use and route of

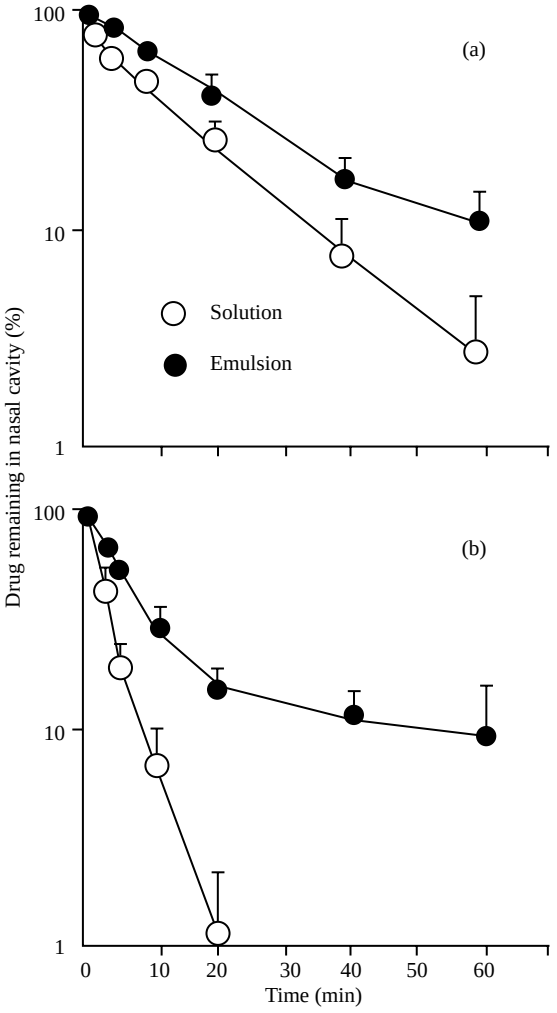

Fig. 2 Disappearance profiles of (a) tetrahydrozoline hydrochloride and (b) chlorpheniramine maleate from rat nasal cavity after nasal administration of an o/w emulsion and an aqueous solution at pH 8. (From Ref. 25.)

administration. Potential toxicity and chemical incompatibilities in the final formulation must be taken into account as must processing details for these also affect the variables that control emulsion stability and therapeutic response such as droplet size distributions and rheology. The design of stable emulsions with the correct pharmacokinetic characteristics and tissue distribution is currently an area of enormous interest, particularly for parenteral IV emulsions. Immediately after injection, the surface of the parenteral emulsion droplets is altered by adsorption of blood components (optosonation) and they are then distributed rapidly through the circulation. Their subsequent fate depends on whether they are treated by the body in the same manner as chylomicrons, or whether they are recognized as foreign particles and cleared by the RES. Many factors, including droplet size and charge, the type of lipid, and the emulsifier composition influence their fate. A major factor to be considered in the formulation of oral preparations is the low pH and high ionic strength of stomach fluids, which may destabilize the emulsion by its effect on the emulsifier.

Pharmaceutical Oils

Oils used in the preparation of pharmaceutical emulsions are of various chemical types, including simple esters, fixed and volatile oils, hydrocarbons, and turpenoid derivatives. The oil itself may be the medicament, it may function as a carrier for a drug, or even form part of a mixed emulsifier system as in the case of some fixed oils that contain sufficient free fatty acids. Many oils, particularly those of vegetable origin, are liable to autooxidation with subsequent rancidity, and it is frequently necessary to add an antioxidant and/or preservative to inhibit this degradation process. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. The most widely used oils in oral preparations are nonbiodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g., arachis, cottonseed, and maize oils) as nutritional supplements.

The choice of oil is severely limited in emulsions for parenteral administration for reasons of toxicity. Purified soybean, sesame, safflower, and cottonseed oils composed mainly of long-chain triglycerides have been used for many years as they are resistant to rancidity and show few clinical side effects. More recently, it has been recognized that the structure of the oil will influence the fate of emulsion droplets after injection. Mixtures containing both long- and medium-chain triglycerides are not only better energy sources for nutritional purposes but they are also cleared more rapidly from the circulation (27); such mixtures are now used in commercial preparations (c.f. Table 1). Structured triglycerides, formed by modifying the oil enzymatically to produce 1,3-specific triglycerides are an area of increasing interest because of their influence on the in vivo circulation time of an emulsion (28). Purified mineral oil is used in some water-in-oil depot preparations where mineral toxicity (e.g., abscess formation at the injection site) must be carefully balanced against efficiency. Emulsified perfluorochemicals are considered acceptable for IV use provided that they are

excreted relatively fast. A major problem in the formulation of the early perfluorocarbon emulsions was that the oils that form the most stable emulsions were not cleared rapidly from the body.

Pharmaceutical Emulsifiers

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can very from days for extemporaneously prepared emulsions to months or years for commercial preparations. In practice, combinations of emulsifiers rather than single agents are used. The emulsifier also influences the in vivo fate of lipid parenteral emulsions by its influence on the surface properties of the droplets and on the droplet size distributions. For convenience, most pharmacy texts classify emulsifiers into three groups: i) surface active agents, ii) natural (macromolecular) polymers, and iii) finely divided solids.

Surface Active Agents

The range of surfactant emulsifiers used in pharmaceutical preparations is illustrated in Table 2. Surfactants are manufactured from a variety of natural and synthetic sources and consequently they show considerable batch-to-batch variations in their homologue compositions and in trace impurities from the starting material. For example, batch variations in the number of neutral phospholipids occur in lecithin surfactants and nonionic polyethylene surfactants show variations in the number of moles of ethylene oxide. The mechanisms by which such batch variations lead to differences in emulsifying properties are now better understood (29).

Although synthetic and semisynthetic surfactants form by far the largest group of emulsifiers studied in the scientific literature and many of them are available commercially, their use in pharmaceutical emulsions is limited by the fact that the majority are toxic (i.e., haemolytic) and irritant to the skin and mucous

Table 2 Synthetic surface active emulsifying agents

Class	Example	Type	Compatibility
Anionic			Efficient to various degrees above pH 7; incompatible with cationic surfactants and polyvalent cations
Alkali and ammonium soaps	Sodium stearate	o/w	
Divalent and trivalent metallic soaps	Calcium oleate	w/o	
Organic sulfates	Sodium lauryl sulfate	o/w	
Cationic			Efficient below pH 7; incompatible with anionic surfactants and polyvalent anions
Quaternary ammonium compounds	Cetrimonium bromide	o/w	
Pyridium compounds	Hexadecyl pyridinium chloride	o/w	
Nonionic			Efficient to various degrees over pH range 4–8; good tolerance to ionic surfactants and polyvalent ions
Alcohol polyethylene glycol ethers	Ceteth 20	o/w	
Fatty acid polyethylene glycol esters	Polyethylene glycol 40 stearate	o/w	
Ethoxylated fatty acid polyethylene glycol esters	Sorbitan mono-oleate (Span 80)	w/o	
	Polyoxyethylene sorbitan monooleate (Tween 80)	o/w	
Polymeric			
Polyoxyethylene-polyoxypropylene block co-polymers	Poloxomers, Pluronic F-68®	o/w	
Amphiphiles			Generally used combined with a surfactant to form a o/w emulsion
Fatty alcohols	Cetyl alcohol	w/o	
Fatty acids	Stearic acid	w/o	

membranes of the gastrointestinal tract. In general, cationic surfactants are the most toxic and irritant and nonionic surfactants the least. Surfactants are therefore used mainly at relatively low concentrations in topical preparations. The quaternary ammonium compounds constitute an important group of cationic emulsifiers in dermatological preparations because they have antimicrobial properties in addition to their o/w emulsifying action. There are many nonionic surfactants with different oil and water solubilities available commercially because for each fatty starting material the polyoxyethylene chain length can be modified by the systematic addition of ethylene oxide groups. However, a limited number of polysorbate surfactants are used in oral emulsions, and parenteral preparations appear to be based only on the lecithins from plant or animal sources and the nonionic polyoxyethylene oxide/polyoxypropylene oxide block copolymer poloxomer 188 (Poloxamer F68®), although some patients using the first generation of perfluorochemical emulsions were sensitive to this poloxomer. The emulsifier influences both emulsion stability and in vivo disposition by its influence on droplet surface properties.

Natural macromolecular materials and finely divided solids

Materials derived from natural sources (Table 3) may originate from animal or vegetable sources and many of these products are susceptible to degradation. For example, depolymerization (the polysaccharides) or hydrolysis (the steroids) usually lead to loss in emulsifying power. Some of these materials, polysaccharides and proteins in particular, provide good culture medium for microorganisms, and therefore preservation of emulsions containing them is imperative. To overcome these problems, a number of purified and semisynthetic derivatives are available, including various purified wool fat derivatives and semisynthetic celluloses such as methylcellulose and sodium carboxymethylcellulose. These are generally more stable than the unmodified materials. These celluloses are used in oral preparations; they are less suitable for topicals because of their unpleasant feel. Finely divided solids such as clays are used in dermatological preparations as structuring agents.

Preservatives

It is essential that emulsions are formulated to resist microbial attack, as this not only can affect the physicochemical properties of the formulation, causing color, odor, or pH changes and even phase separation, but may also constitute a health hazard. The potential sources of contamination can be from raw materials (especially if these are natural products), water, manufacturing and packaging equipment, or patients themselves. W/o emulsions are less susceptible to attack than o/w emulsions because the aqueous continuous external phase can produce ideal conditions for the growth of bacteria, moulds, and fungi. Preservatives are not used in parenteral emulsions, which are sterilized, generally by autoclaving, but sometimes by using sterile components and aseptically assembling the final emulsion.

There is no simple way of predicting the ideal preservative for a particular emulsion. In addition to requiring a wide spectrum of activity against bacteria, yeasts, and molds, the preservative should be free from toxic, irritant, or sensitizing activity. Some commonly used preservatives in oral and topical preparations include phenoxyethanol, benzoic acid, parabenzoates, and chlorcresol. Emulsions are heterogeneous products, and the

Table 3 Emulsifying agents derived from natural products and finely divided solids

Class	Example	Emulsion type, route of administration	Comments
Polysaccharide	Acacia	o/w; oral	Stable over a wide pH range
	Carageen	o/w; oral	As above
	Methylcellulose	o/w; oral, parenteral	As above, less prone to hydrolysis
Protein	Gelatin	o/w; oral,	Emulsifying properties pH dependent
Glycoside	Saponin	o/w; topical	
Phospholipid	Lecithin	o/w; oral, parenteral	Emulsifying properties dependent on number of negative lipids
Sterol	Wool fat	w/o; topical	Poor emulsifiers alone
	Cholesterol and its esters	w/o; topical	As above
Finely divided solids	Bentonite	o/w and w/o; topical	Gelation dependent on processing conditions
	Veegum	o/w; oral, topical	As above
	Aluminium hydroxide	o/w; oral	

preservative partitions between the oil and aqueous phases. As a sufficient aqueous concentration of the active (usually unionized) form must be present to ensure proper preservation, pH is an additional factor to be considered. Problems often arise because many of the materials used in emulsion formulation, for example hydrocolloids or polyoxyethylene surfactants, can interact with the preservatives, thus depleting their activity. The use of a single preservative is often considered unrealistic, and attention is being increasingly focused on the use of mixtures for a wider spectrum of activity, although this may introduce additional compatibility problems.

Antioxidants and Humectants

Antioxidants are added to many pharmaceutical preparations to prevent oxidative deterioration on storage of the oil, emulsifier, or the drug itself. Such deterioration, as well as destabilizing the formulation, imparts an unpleasant odor or taste. Some oils are supplied containing antioxidants already. Those commonly used in pharmacy include butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) at concentrations up to 0.2%, and the alkyl gallates. Humectants such as propylene glycol, glycerol, and sorbitol (5%) are often added to dermatological preparations to reduce the evaporation of water from the emulsion during storage and use. They are sometimes claimed to prevent evaporation of water from the surface of the skin, although their use at high concentrations would be expected to have the opposite effect (i.e., remove moisture and dehydrate the skin).

EMULSION FORMATION

There are essentially two major considerations in emulsification: first, the formation of emulsions of the correct type, oil-in-water, water-in-oil, or multiple emulsion with the required droplet size distributions and second, the stabilization of the dispersed droplets so formed. When given amounts of two immiscible liquids are mixed or mechanically agitated in the absence of other additives, both phases tend to form droplets of various sizes. The size distributions are related to the forces involved during the agitation process, and the number of droplets of each liquid depends on its relative volume. The surface free energy of the system, which is dependent on both total surface area and interfacial tension is raised by the increase in surface area produced during dispersion, and the system is thermodynamically unstable. To reduce this, high-energy droplets first assume a spherical shape, as this gives the minimum surface area for a given volume, and then on collision the droplets will coalesce (fuse) to reduce the interfacial area, the interfacial tension remaining constant.

The type of emulsion that forms, either o/w or w/o, depends on the relative rates of coalescence of each type of droplet, with the more rapidly coalescing droplets forming the continuous phase. Generally, this is the liquid present in the larger amount because higher number of droplets increase the probability of collision and coalescence. With phase volumes of oil and water close to 50%, other factors such as the order and rate of addition of each liquid are important. If agitation ceases, coalescence will continue until complete phase separation—the state of minimum free energy—is reached. Thus, emulsification can be considered as the result of two competing processes, namely the disruption of bulk liquids to produce fine droplets and the recombination of the droplets to give back the original bulk liquids. With the inclusion of surfactants or other classes of emulsifiers, the type of emulsion that forms is no longer simply a function of the phase volume and the order of mixing, but also the relative solubilities of the emulsifier in oil and water. In general, the phase in which the emulsifier is most soluble becomes the continuous phase (Bancroft's Rule); thus, hydrophilic polymers and surfactants promote o/w emulsions whereas lipophilic surfactants promote w/o emulsions. Preferential coalescence of the phase in which the emulsifier is most soluble occurs because when droplets collide, the emulsifier is easily displaced from the interface into the droplet, thus providing little protection against coalescence. Theoretically, the disperse phase of an emulsion can occupy up to 74% of the phase volume, and such high internal phase o/w emulsions have been produced with suitable surfactants. It is more difficult to formulate w/o emulsions with greater than 50% disperse phase because of the steric mechanisms involved in their stabilization (discussed later), and the addition of extra water sometimes causes inversion to an o/w emulsion.

Emulsion Characteristics

In general, an emulsion exhibits the characteristics of its external phase. Several methods are available for identifying the emulsion type. Dilution tests are based on the fact that the emulsion is only miscible with the liquid that forms its continuous phase. Conductivity measurements rely on the poor conductivity of oil compared with water, and give low values in w/o emulsions where oil is the continuous phase. Staining tests in which a water-soluble dye is sprinkled onto the surface of the emulsion also indicate the nature of the continuous phase. With an o/w emulsion there is rapid incorporation of the dye into

the system whereas with the w/o emulsion the dye forms microscopically visible clumps. The reverse happens on addition of an oil-soluble dye. These tests essentially identify the continuous phase and do not indicate whether a multiple emulsion has been produced. This can be resolved by microscopy.

Rheology

The rheological properties of emulsions are influenced by a number of interacting factors, including the nature of the continuous phase, the phase volume ratio, and to a lesser extent, particle size distributions. A variety of products ranging from mobile liquids to thick semisolids can be formulated by altering the dispersed phase volume and/or the nature and concentration of the emulsifiers. For low internal phase volume emulsions, the consistency of the emulsion is generally similar to that of the continuous phase; thus, w/o emulsions are generally thicker than o/w emulsions, and the consistency of an o/w system is increased by the addition of gums, clays, and other thickening agents that import plastic or pseudoplastic flow properties. Some mixed emulsifiers interact in water to form a viscoelastic continuous phase to give a semisolid o/w cream (7).

Droplet Size Distributions

Droplet size distributions in pharmaceutical emulsions are important from both stability and biopharmaceutical considerations. The larger the particle size, the greater the tendency to coalesce and further increase droplet size. Thus, fine particles generally promote better stability. Size distributions are influenced by the characteristics of the emulsifier and the method of manufacture. From a biological point of view, fine emulsification enhances gastrointestinal absorption and whilst this is desirable with oral formulations of nutrient oils alone or with drugs dissolved in them, it may give adverse clinical effects with mineral oils that are used for a local effect and are toxic if absorbed. Droplets in emulsions used as contrast media in computed tomography are approximately 1–3 μm. Parenteral emulsions should be formulated so that the dispersed droplet sizes range from approximately 100 nm to 1 μm. In any event, sizes should never be greater than 5 μm in diameter because of the danger of pulmonary emboli. There is clear evidence that, as with other colloidal preparations, droplet size distributions influence the clearance kinetics of parenteral emulsions. Larger droplets are treated as foreign bodies and rapidly cleared by elements of the RES while smaller droplets may be treated as natural fat sorting lipoproteins, with a different in vivo fate (30). Drug delivery from dermatological preparations also appears to be improved in lipid emulsions containing submicron droplets (11).

EMULSION STABILITY

A stable emulsion is considered to be one in which the dispersed droplets retain their initial character and remain uniformly distributed throughout the continuous phase for the desired shelf life. There should be no phase changes or microbial contamination on storage, and the emulsion should maintain elegance with respect to odor, color, and consistency. Instabilities of both chemical and physical origins can occur in emulsion formulations. Chemical instabilities, such as the development of rancidity in natural oils due to oxidation by atmospheric oxygen, the depolymerization of macromolecular emulsifiers by hydrolysis, or microbial degradation can be minimized by the addition of suitable antioxidants and preservatives. More general chemical instabilities involving interactions between the drug and emulsion excipients or between the excipients themselves may lead to physical instabilities. If these interactions involve the emulsifying agent, they may destroy its emulsifying properties, causing the emulsion to break. For example, interactions between phenolic preservatives and polyoxyethylene nonionic emulsifiers may lead to loss of emulsifying power as well as poor preservation.

Physical Instability

As emulsions are inherently unstable, they eventually revert to the original state of two separate liquids, that is, will break or crack. In the presence of an emulsifier and other additives, this state is approached via several distinct processes, some of which are reversible such as creaming and flocculation and others irreversible such as coalescence and Ostwald ripening. Phase inversion when an oil-in-water emulsion inverts to form a water-in-oil emulsion or visa versa is a special case of irreversible instability that occurs only under well-defined conditions such as a change in emulsifier solubility due to specific interactions with additives or to a change in temperature (Fig. 3).

Flocculation describes a weak reversible association between emulsion globules separated by thin films of continuous phase. The individual droplets retain their separate identities, but each floccule or cluster of droplets behaves physically as a single unit. The association arises from the interaction of attractive and repulsive forces

between droplets and is reversible in the sense that the original dispersion can generally be regained by mild agitation. Flocculation is generally regarded as a precursor to the irreversible process of coalescence, although sometimes the time scale between flocculation and coalescence can be extended almost indefinitely by the adsorbed emulsifier, giving a kinetically stable emulsion.

Coalescence, where dispersed phase droplets merge to form larger droplets, takes place in two distinct stages. It begins with the drainage of liquid films of continuous phase from between the oil droplets as they approach one another and ends with the rupture of the film when a critical thickness is reached. The approaching droplets may deform as the opposing surfaces distort to either flatten (small droplets) or dimple (larger droplets) under the hydrodynamic pressures generated by viscous flow of the continuous phase.

Coalescence is not the only mechanism by which dispersed phase droplets increase in size. If the emulsion is polydispersed and there is significant miscibility between the oil and water phases, then Ostwald ripening, where droplet sizes increase due to large droplets growing at the expense of smaller ones, may also occur. This destabilizing process is a result of the Kelvin effect and occurs when small emulsion droplets (less than 1 μm) have higher solubilities (and vapor pressures) than do larger droplets (i.e. the bulk material) and consequently are thermodynamically unstable. To reach the state of equilibrium, molecules from these droplets dissolve and diffuse through the continuous phase to enlarge the larger droplets. As the small droplets lose their oil, they become even smaller, the vapor pressure difference increases, and Ostwald ripening is further enhanced.

Creaming or sedimentation occurs when the dispersed droplets or floccules separate under the influence of gravity to form a layer of more concentrated emulsion, the cream. Generally a creamed emulsion can be restored to its original state by gentle agitation. This process, which

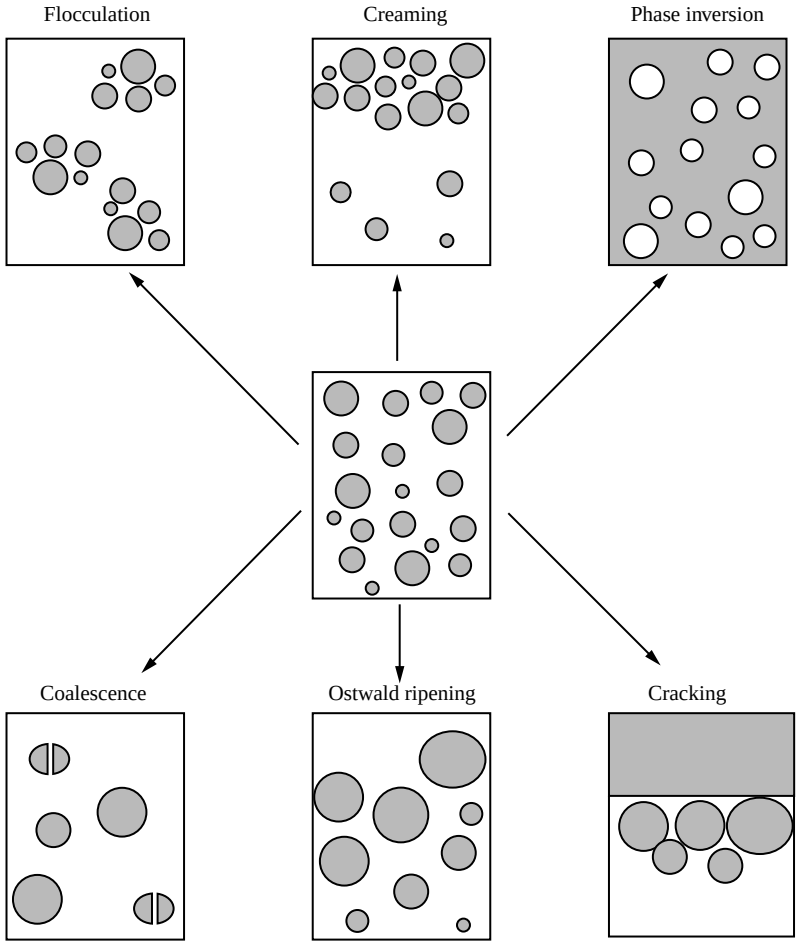

Fig. 3 Schematic representation of the various processes of emulsion breakdown.

inevitably occurs in any dilute emulsion if there is a density difference between the phases as a consequence of Stokes law, should not be confused with flocculation which is due to particle interactions resulting from the balance of attractive and repulsive forces. Most oils are less dense than water so that the oil droplets in o/w emulsions rise to the surface to form an upper layer of cream. In w/o emulsions, the cream results from sedimentation of water droplets and forms the lower layer. According to Stokes Law, the rate of creaming can be minimized by reducing droplet sizes and/or thickening the continuous phase. Adjustment of the densities of the two phases has received little attention.

The destabilization processes are not independent and each may influence or be influenced by the others. For example, the increased droplet sizes after coalescence or Ostwald ripening will enhance the rate of creaming, as will the formation of large floccules which behave as single entities. In practice, creaming, flocculation, and Ostwald ripening may proceed simultaneously or in any order followed by coalescence.

Coalescence and Ostwald ripening are obviously the most serious types of instability as they result in the formation of progressively larger droplets and ultimately lead to phase separation. Creaming and flocculation, on the other hand, are more subtle forms of instability, for although they represent potential steps towards coalescence and breaking due to the close proximity of the droplets, many practical emulsions remain in this state for long periods of time without significant coalescence and can be redispersed simply by shaking the container.

EMULSION STABILIZATION

Emulsifiers stabilize emulsions in a number of different ways, all of which act to prevent or delay the various destabilization processes described previously. The emulsifier may form an interfacial film at the oil–water interface and/or structure (i.e., thicken) the continuous phase. The interfacial film introduces additional repulsive (e.g., electrostatic, steric, or hydrational) forces between droplets to counteract attractive van der Waals forces and inhibit the close approach of droplets. It may also provide a barrier to the coalescence of droplets in close proximity, particularly if the film is close-packed and elastic. Surfactant interfacial films also lower the interfacial tension between oil and water. Although this effect is important during the emulsification process where it facilitates the breakup of droplets, it is not a major factor in maintaining the long-term stability of emulsions. In emulsions that are thickened by the emulsifier, the interfacial film does not play the dominant role in maintaining stability; rather, it is the structured continuous phase that forms a rheological barrier to prevent the movement and hence the close approach of droplets and also inhibits Ostwald ripening.

Classical (Interfacial) Theories

Classical theories of emulsion stability focus on the manner in which the adsorbed emulsifier film influences the processes of flocculation and coalescence by modifying the forces between dispersed emulsion droplets. They do not consider the possibility of Ostwald ripening or creaming nor the influence that the emulsifier may have on continuous phase rheology. As two droplets approach one another, they experience strong van der Waals forces of attraction, which tend to pull them even closer together. The adsorbed emulsifier stabilizes the system by the introduction of additional repulsive forces (e.g., electrostatic or steric) that counteract the attractive van der Waals forces and prevent the close approach of droplets. Electrostatic effects are particularly important with ionic emulsifiers whereas steric effects dominate with nonionic polymers and surfactants, and in w/o emulsions. The applications of colloid theory to emulsions stabilized by ionic and nonionic surfactants have been reviewed as have more general aspects of the polymeric stabilization of dispersions (4, 31, 32).

The DLVO theory, which was developed independently by Derjaguin and Landau and by Verwey and Overbeek to analyze quantitatively the influence of electrostatic forces on the stability of lyophobic colloidal particles, has been adapted to describe the influence of similar forces on the flocculation and stability of simple model emulsions stabilized by ionic emulsifiers. The charge on the surface of emulsion droplets arises from ionization of the hydrophilic part of the adsorbed surfactant and gives rise to electrical double layers. Theoretical equations, which were originally developed to deal with monodispersed inorganic solids of diameters less than 1 μm, have to be extensively modified when applied to even the simplest of emulsions, because the adsorbed emulsifier is of finite thickness and droplets, unlike solids, can deform and coalesce. Washington (33) has pointed out that in lipid emulsions, an additional repulsive force not considered by the theory due to the solvent at close distances is also important.

The theory states that the forces between droplets can be considered as the sum of an attractive van der Waals part V_A and a repulsive electrostatic part V_R when identical electrical double layers overlap. As the origin of each force is independent of the other, each is evaluated separately, and the total potential of interaction V_T between the two

droplets as a function of their surface-to-surface separation is obtained by summation

$$V_T = V_A + V_R$$

A schematic potential energy of interaction with distance plot is shown in Fig. 4a. It can be seen that a weak attraction occurs at large droplet separations represented by the secondary energy minimum, and a very strong attraction at small droplet separations hence the very deep primary minimum. At intermediate distances, double-layer repulsion dominates and there is a maximum in the curve. Flocculation occurs in the secondary minimum, where the attractive forces are relatively weak and floccules are easily separated by low energy agitation. Once flocculated, droplets are prevented from approaching closer by the potential energy barrier. If they have sufficient energy to overcome the barrier, the process of coalescence commences as the droplets move closer together. Once in the primary minimum the aggregates formed are separated by only a small distance so that stability against coalescence is determined by the resistance of the interfacial film to rupture.

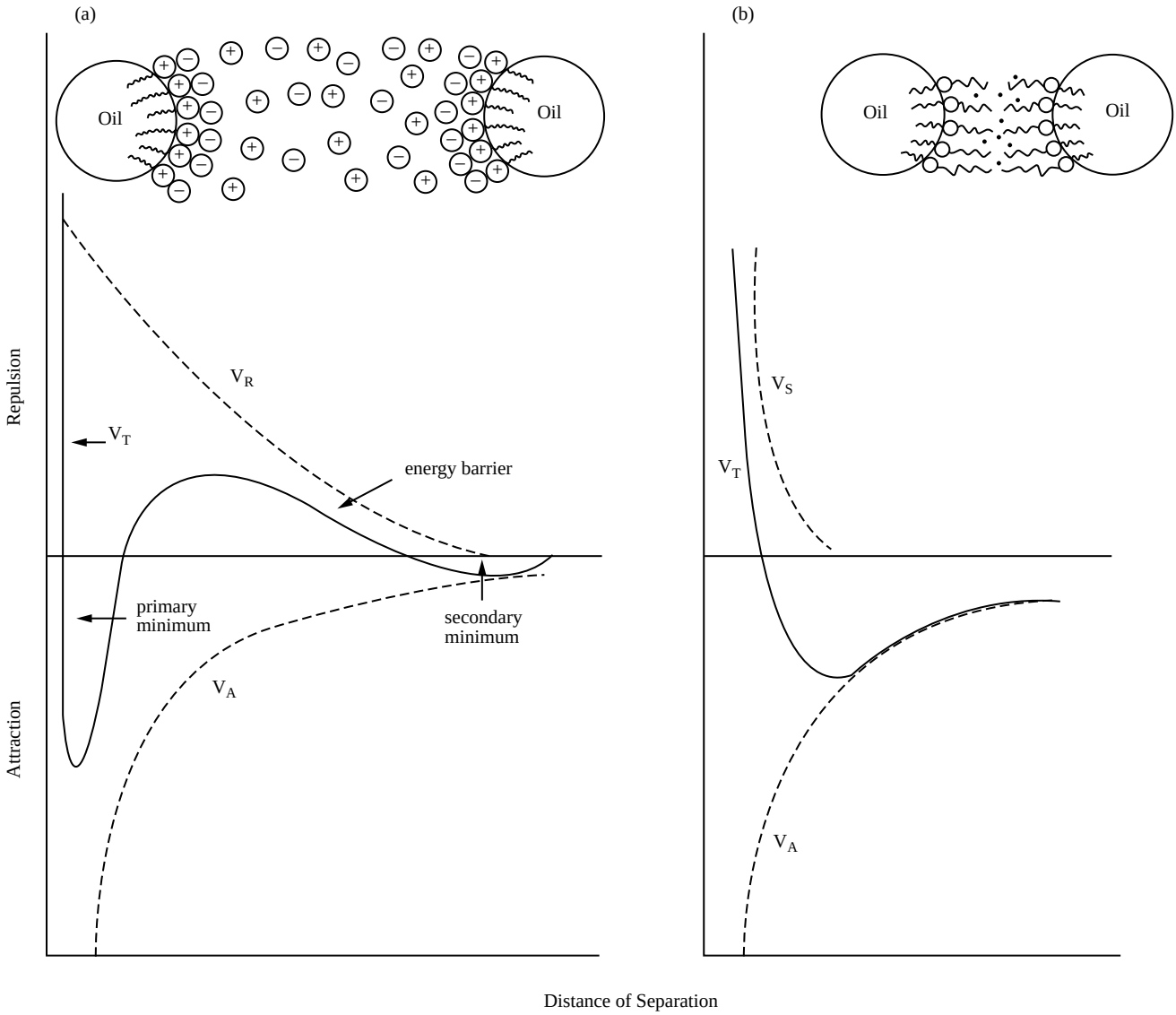

Fig. 4 The total potential energy of interaction V_T as a function of distance of surface separation H for two similar oil droplets in an oil-in-water emulsion. (a) Electrostatic stabilization by a monolayer of ionic surfactant. (b) Steric stabilization by a monolayer of nonionic surfactant. V_A: van der Waals attractive force; V_R: electrostatic repulsive force; V_S: steric repulsive force.

The height of the energy barrier, which is crucial to emulsion stabilization, depends on the state of ionization of the emulsifying agent. Most surfactants are used at pH values where they are totally ionized so that the surface potential is high, giving a correspondingly high energy barrier. The surface potential cannot be measured directly, but can be estimated from the experimentally derived zeta potential. In lipid emulsions for parenteral nutrition, the electrostatic barrier is provided by the ionization of the negatively charged phospholipids in the emulsifier film at the oil droplet–water interface. At physiological pH, a typical fat emulsion carries a negative charge with the zeta potential between 30 and 60 mV. This is sufficient to ensure stability because of the high potential energy barrier. The addition of electrolytes or a change in pH can have a devastating effect on emulsion stability by compressing the double layers, thus reducing the zeta potential and energy barrier and allowing droplets to move into the primary minimum. Thus, great care must be exercised when electrolytes are added nutritional emulsions. With emulsifiers such as proteins and gums, ionization, and hence emulsifying activity, is also pH dependent (c.f. Table 3).

The DLVO theory does not explain either the stability of water-in-oil emulsions or the stability of oil-in-water emulsions stabilized by adsorbed nonionic surfactants and polymers where the electrical contributions are often of secondary importance. In these, steric and hydrational forces, which arise from the loss of entropy when adsorbed polymer layers or hydrated chains of nonionic polyether surfactant intermingle on close approach of two similar droplets, are more important (Fig. 4b). In emulsions stabilized by polyether surfactants, these interactions assume importance at very close distances of approach and are influenced markedly by temperature and degree of hydration of the polyoxyethylene chains. With block copolymers of the ethylene oxide–propylene oxide type, such as the poloxamers, the hydrated polyoxyethylene chains extend into the continuous phase to provide steric stabilization and the hydrophobic propylene oxide portion is anchored onto the droplet surface to form a strong protecting layer against coalescence. Stability is optimized when the droplet surfaces are completely coated by polymer chains so that desorption and lateral movement of the polymer is inhibited. With w/o emulsions, steric hindrance of the adsorbed chains of emulsifier can also result in entropic repulsion effects at small distances of separation.

Some natural polymeric emulsifiers such as the gums, in addition to forming steric and electrostatic barriers form thick multilayered films that are very resistant to film rupture. They may also thicken the continuous phases of o/w emulsions, thereby reducing the rate of film drainage in the initial stages of coalescence. Small solid particles may stabilize emulsions if they are wetted by both phases and possess sufficient adhesion for one another to form a coherent interfacial film. The film serves as a mechanical barrier to prevent the coalescence of droplets, and if charged, electrostatic mechanisms further assist in the stabilization of the emulsion. Although solids are not generally sufficient to stabilize emulsions on their own, they often reinforce the effectiveness of other emulsifiers.

Stabilization by Mixtures of Emulsifiers

Most pharmaceutical emulsions, whether dilute mobile systems for internal use or thick semisolid creams for application to the skin, contain mixtures of emulsifiers, as these provide more stable preparations. For example, traditional oral preparations are sometimes stabilized by mixtures of gums such as acacia and tragacanth and mixtures of nonionic surfactants of high and low hydrophile–lipophile balance (HLB) generally form more stable emulsions than a single surfactant. The lecithins used to stabilize parenteral emulsions are usually mixtures of neutral and charged lipids as are the partially neutralized glyceryl esters such as self-emulsifying glyceryl monostearate. Combinations of sparingly soluble long-chain acids, alcohols, or glyceryl esters with more soluble ionic and non-ionic surfactants are widely used in dermatological o/w lotions and creams, where they are sometimes added in the form of a preblended emulsifying wax (Table 4). Surfactant/fatty acid combinations are also present in traditional liniment and lotion emulsion formulations prepared by the nascent soap method and in preparations where triethanolamine soaps are formed in situ from the interaction of triethanolamine and excess fatty acid.

Equations from the DLVO theory even if modified to allow for the steric repulsive forces cannot cope with mixtures of emulsifiers. Increased stability in model emulsions (c.f. Fig. 1a) is attributed not so much to the control of flocculation (although this does occur), but rather to the prevention or retardation of coalescence by closer packing of the molecules in the adsorbed monolayer to form a more rigid and condensed film. There is now substantial evidence that interactions between emulsifier components to form specific lamellar phases, either liquid crystalline or gel, that are capable of incorporating large volumes of water are important for the stability of many parenteral and dermatological emulsions. Mobile parenteral injections stabilized by

Table 4 Typical emulsifying waxes and their component surfactants

Emulsifying wax	Components
Emulsifying wax USNF	Cetearyl alcohol, polysorbate
Cationic emulsifying wax BP	Cetearyl alcohol, cetrimonium bromide
Cetomacrogol emulsifying wax BP	Cetearyl alcohol, ceteth 20
Glyceryl stearate, SE	Glyceryl stearate, soap

phospholipid mixtures usually contain swollen lamellar liquid crystals (34) whereas a swollen gel phase which generally provides better stability as well as a means of controlling rheological properties dominates in semisolid dermatological emulsions prepared with emulsifying waxes. The relevance of bilayer gel and liquid crystalline phases in dermatological and parenteral emulsions have been discussed in reviews (10, 29). Much of the information about their structures was obtained from investigations of the phase behaviour of emulsifiers and their components in water over the ranges of concentration and temperature relevant to the manufacture, storage, and use of the formulations. It is interesting to note that the same electrostatic, hydrational, and steric forces that operate in simple emulsions also dominate the stability and properties of the lamellar phases (35).

Ostwald Ripening

Ostwald ripening has not been studied as extensively in emulsions as has coalescence, although it is a major mechanism for instability in lipid and perfluorochemical emulsions with submicron droplet sizes where a condensed monolayer is not always necessary for emulsion stability (36). Although surfactant interfacial films protect against flocculation and coalescence, Ostwald ripening may in fact be enhanced if the surfactant is above the critical micelle concentration (cmc) because of the diffusion of solubilized oil through the continuous phase. The addition of a third component to the emulsion that has a lower vapor pressure and solubility than the disperse phase has will also inhibit Ostwald ripening. The addition of long-chain alkanes to comparatively unstable oil-in-water emulsions prepared with sodium dodecyl sulfate resulted in marked increases in stability even though the alkanes do not effect the composition or mechanical properties of the oil–water interface (37). The stability of pure perfluorodecalin emulsions used as blood substitutes is enhanced by the addition of a small quantity of perfluorotributylamine, and lipid emulsions containing local anaesthetic/analgesic drugs show enhanced stability in the presence of hydrophobic excipients of lower solubility than the disperse phase (38). Polymeric emulsifiers possibly stabilize emulsions against Ostwald ripening by increasing the viscosity of the continuous phase. The relative lack of Ostwald ripening in emulsions prepared from oils immiscible with water, such as mineral oil, may partly explain why they are easier to emulsify than are more miscible vegetable oils used in parenteral preparations.

Selection of Emulsifier

Over the years there have been many attempts to find systemic methods for screening potential emulsifiers from the enormous number of surfactants available commercially. Although the mechanisms governing the stability of emulsions, including the complex multiple phase systems of pharmacy are becoming clearer, there are still few scientific guidelines to assist in the proper selection of emulsifiers for a particular emulsion. Semiempirical methods based on both interfacial considerations and the phase behavior of the emulsifiers are considered briefly next.

The hydrophile–lipophile balance (HLB) concept

Griffin devised the concept of hydrophile–lipophile balance (HLB) and its additivity many years ago for selection of nonionic emulsifiers and this rather empirical method is still widely used. The enormous literature on the HLB of surfactants has been reviewed by Becher (39). Each surfactant is allocated an HLB number usually on a scale of 0–20, based on the relative proportions of the hydrophilic and hydrophobic part of a molecule. Water-in-oil emulsions are formed generally from oil-soluble surfactants of low HLB number and oil-in-water emulsions from more hydrophilic surfactants of high HLB number. The method of selection is based on the observation that each type of oil will require an emulsifying agent of a specific HLB number to produce a stable emulsion. Thus, oils are often designated two "required" HLB numbers, one low and one high, for their emulsification to form water-in-oil and oil-in-water

emulsions respectively. A series of emulsifiers and their blends with HLB values close to the required HLB of the oil are then examined to see which one forms the most stable emulsion (c.f. Fig. 1a).

Although the HLB concept narrows the range of emulsifiers to select and provides a schematic approach for the formulator, it is limited by its strict relation to molecular structure of the individual surfactants. The concept does not consider the total emulsion and is therefore insensitive to interactions between emulsifier components, the influence of temperature changes, or the presence of additional ingredients in the emulsion. Consequently, not all emulsifier blends of the correct HLB form stable systems. For example, when surfactants of widely different HLB numbers are blended to give the optimum theoretical HLB, the high solubility of the surfactant in the oil and aqueous phases change the balance of the molecules at the interface and unstable emulsions may result. Similarly, if the added surfactants form intermolecular associations at the interface, the association complex is unlikely to have properties that are related in any simple way to the individual properties of the constituent molecules.

The phase inversion temperature (PIT) method (HLB-temperature)

A complementary means of emulsifier selection, the phase inversion temperature (PIT), which employs a characteristic property of the emulsion rather than the properties of the emulsifiers in isolation, was introduced by Shinoda (40). The method uses the fact that the stabilities of oil-in-water emulsions containing nonionic surfactants are closely related to the degree of hydration of the interfacial films. Emulsion stability is reduced by increase in temperature or added salts because these decrease the extent of interfacial film hydration. Phase inversion, due to a change from preferential water solubility of the emulsifier film at low temperature to preferential oil solubility at high temperature, will occur at a specific temperature unique to the particular emulsion and this can be determined experimentally. As a general rule, relatively stable oil-in-water emulsions are obtained when their temperatures during storage and use are between 20 and 65°C below the PIT, presumably because the films are sufficiently hydrated. Mixtures of emulsifiers with identical HLBs produce emulsions with quite different PITs because additives and interactions between the components affect PIT but not HLB.

Microscopic selection for multiple phase emulsions

The better understanding of the mechanisms of stability in complex dermatological emulsions stabilized by surfactants and amphiphiles has enabled the development of a rapid microscopic method for evaluation of potential emulsifiers. The method is based on the observation that good emulsifier blends that stabilize emulsions by the formation of multilayers of stable gel phase also swell spontaneously in water at ambient temperature and this process can be observed microscopically. Mixtures that do not form gel phase or form metastable gels only after a heating and cooling cycle cannot be observed to swell spontaneously at ambient temperature (4).

Emulsification Techniques

Emulsions are usually prepared by the application of mechanical energy produced by a wide range of agitation techniques. These disrupt droplets by the application of either shear forces in laminar flow or inertial forces in turbulent flow. Emulsifying devices ranging from simple hand mixers and stirrers to the use of propeller or turbine mixers, static mixers, colloid mills, homogenizers, and ultrasonic devices have been used.

Emulsifiers also have an important role in the process of emulsification. Surfactant emulsifiers reduce interfacial tensions during emulsification, making droplets easier to break up as well as reducing the tendency for recombination. Other emulsifiers such as the polymer macromolecules alter the hydrodynamic forces during the agitation process by their influence on rheological properties. Scale-up procedures from the laboratory to manufacture can introduce a number of problems due to the difficulties in matching the exact conditions of mixing, and, because of entrapment-of air, especially in emulsions of high consistency that have a yield value. Along with being inelegant, even traces of atmospheric air can cause decomposition in drugs or excipients susceptible to oxidation.

There are additional constraints when manufacturing parenteral emulsions that must be sterile and of fine particle size. Perfluorochemical and fat emulsions are usually prepared by homogenization at high temperature and pressure, as a large output of energy is required to produce droplet sizes considerably less than 1 μm. Although heat sterilization is widely used, this places a severe test on the stability, and emulsions are sometimes prepared from sterile components under strict aseptic conditions and further sterilized by filtration (15).

Processing variables

Differences in manufacturing techniques such as the rate of the heating and cooling cycle, the extent and order of mixing can cause variations in the consistency and

rheology of the resulting emulsions. The initial particle size of the emulsion depends on the emulsifiers used, the emulsification equipment, the addition speed, and the phase volume. If the surfactant is placed in one of the phases prior to emulsification, it will migrate to the other to establish equilibrium. Thus, emulsification temperatures and cooling rates are important and the time of the mixing should be sufficient to allow the surfactant to migrate to and equilibrate at the interface throughout the process. Oil-in-water emulsions are sometimes prepared by the phase inversion technique, where the aqueous phase is added to the oil phase to form a w/o emulsion that inverts to an o/w emulsion on addition of further amounts of water. This process is claimed to give finer emulsions.

Preparation techniques, in particular cooling rates and mixing procedures, have a marked effect on initial and final consistencies of emulsions prepared with nonionic emulsifying waxes. For example, "shock" cooling and limited mixing initially produces very mobile systems whereas slow cooling with adequate mixing produces semisolid emulsions. Mixing time, when the emulsifiers are in the molten state, influences the distribution of surfactant within the molten masses and bilayers and the relative lamellar order within the system. With ionic emulsifying waxes, different preparation techniques cause comparatively minor variations in the consistency of the final product. It was shown that differences are not due to the gel phase component of cationic ternary systems, but rather due to the variations in size of the crystalline alcohol that precipitates after manufacture. Systems formed by a rapid "shock" cooling method exhibited smaller but greater numbers of cetostearyl alcohol crystals and were thicker than similar ternary systems manufactured by a more lengthy procedure (29).

MICROEMULSIONS

Microemulsions are thermodynamically stable, transparent (or translucent) dispersions of oil and water that are stabilized by an interfacial film of surfactant molecules. The surfactant may be pure, a mixture, or combined with a cosurfactant such as a medium-chain alcohol (e.g., butanol, pentanol). These homogeneous systems, which can be prepared over a wide range of surfactant concentrations and oil to water ratios (20–80%), are all fluids of low viscosity.

The term microemulsion, which implies a close relationship to ordinary emulsions, is misleading because the microemulsion state embraces a number of different microstructures, most of which have little in common with ordinary emulsions. Although microemulsions may be composed of dispersed droplets of either oil or water, it is now accepted that they are essentially stable, single-phase swollen micellar solutions rather than unstable two-phase dispersions. Microemulsions are readily distinguished from normal emulsions by their transparency, their low viscosity, and more fundamentally their thermodynamic stability and ability to form spontaneously. The dividing line, however, between the size of a swollen micelle (~10–140 nm) and a fine emulsion droplet (~100–600 nm) is not well defined, although microemulsions are very labile systems and a microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system. In contrast, ordinary emulsion droplets, however small, exist as individual entities until coalescence or Ostwald ripening occurs.

Figure 5 shows a hypothetical phase diagram with representation of microemulsion structures. At high water concentrations, microemulsions consist of small oil droplets dispersed in water (o/w microemulsion), while at lower water concentrations the situation is reversed and the system consists of water droplets dispersed in oil (w/o microemulsions). In each phase, the oil and water droplets are separated by a surfactant-rich film. In systems containing comparable amounts of oil and water, equilibrium bicontinuous structures in which the oil and the water domains interpenetrate in a more complicated manner are formed. In this region, infinite curved channels of both the oil and the water domains extend over macroscopic distances and the surfactant forms an interface of rapidly fluctuating curvature, but in which the net curvature is near zero.

Pharmaceutical and Biological Applications of Microemulsions

Microemulsions provide ultralow interfacial tensions and large interfacial areas as well as the ability to concentrate and localize significant amounts of both oil- and water-soluble materials within the same isotropic medium. Over the years, attention has been focused on their potential use as novel reaction media for a wide range of chemical, biochemical, and photochemical reactions, and as carriers for chemicals and small particles, reviewed by Eccleston (41). Inverse microemulsions of the w/o type are the subject of particular interest because of the rapidly emerging range of biotechnological applications based on their ability to solubilize enzymes in the water domains without denaturation or loss of activity. The ability of such solubilized hydrophilic enzymes to transform hydrophobic substrates dissolved in the organic

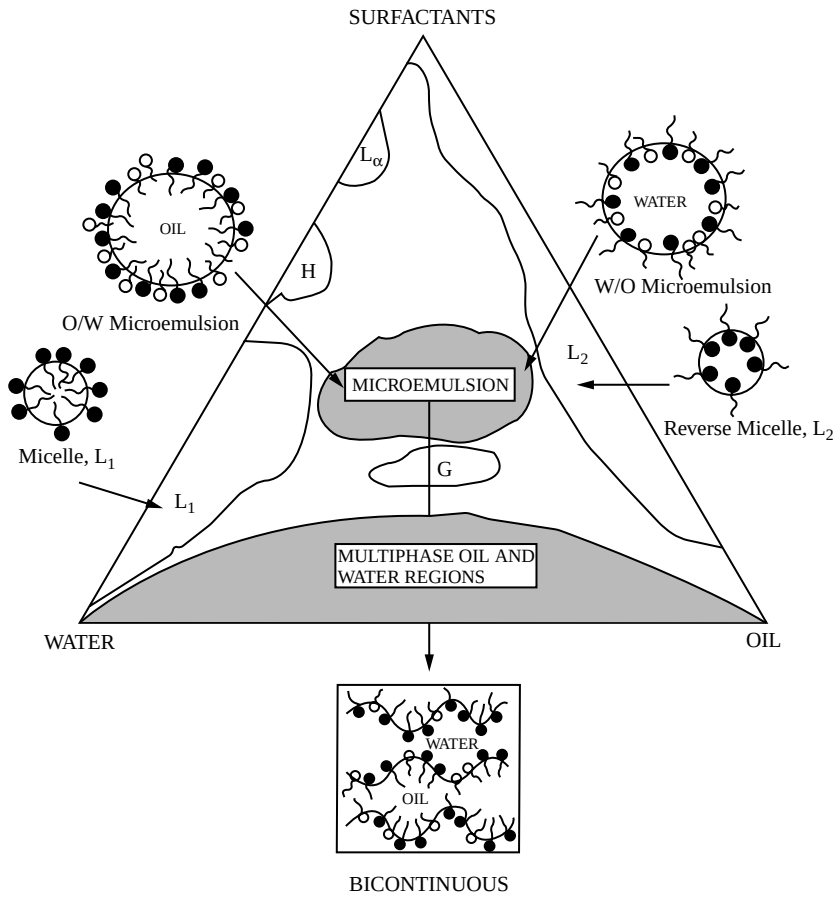

Fig. 5 Ternary phase diagram for oil, water, and surfactant mixtures showing micellar, microemulsion, and multiphase macroemulsion regions with schematic representations of various structures.

phase could lead eventually to the synthesis of new drugs. As with ordinary emulsions, microemulsions show improved gastrointestinal absorption. They also have a number of other advantages over macroemulsions for drug delivery. Microemulsions form spontaneously without the aid of high shear equipment or significant heat input (heat and gentle mixing are required only if it is necessary to melt any of the ingredients) and their microstructures are independent of the order of addition of the excipients. Optical transparency and low viscosity of microemulsions ensure that they are cosmetically elegant and easy to handle and pack, and their indefinite stabilities ensure a long shelf life. Microemulsions have thus attracted much interest in their drug delivery potential. Both o/w and w/o emulsions have been shown to enhance the oral bioavailability of drugs, including various peptides (42). A peroral concentrate of cyclosporine is now available commercially (Sandimmune Neoral® Novartis), which forms a microemulsion in the aqueous fluids of the gastrointestinal tract. In this preparation, the rate of absorption of cyclosporin is more rapid and less variable than it is with the conventional oily dispersion. Calcein administered intraduodenally in the aqueous phase of a w/o microemulsion prepared from medium-chain triglycerides (43) produces significantly higher plasma levels of the drug compared with an aqueous solution.

Microemulsions have also been used for topical delivery where they increase drug absorption. For example, cetyl alcohol, which is commonly used as an emulsifier in lotions and creams, is absorbed faster and deeper into the skin when formulated as a component of a microemulsion (44). Although efficient skin penetration may be desirable for a therapeutic agent, the relatively high concentrations of surfactant (10–25%) and cosurfactant or cosolvent (5–10%) in such formulations could enhance skin absorption of potential irritants or carcinogens. In fact, the main limitations in realizing

the full potential of microemulsions as drug delivery systems are the narrow range of surfactants, cosurfactants, solvents, and other materials acceptable pharmaceutically.

Microemulsion Formation

Many approaches have been used to explore the mechanisms of microemulsion formation and stability [summarized by Eccleston (41) and Attwood (45)]. Early theories considered interfacial aspects of microemulsions and did not distinguish between thermodynamically stable systems and very fine kinetically stable emulsions. For microemulsions to form spontaneously, the free energy involved when the interfacial area is increased, ΔG ($\Delta G = \gamma \Delta A$, where ΔA is the increase in interfacial area) must be negative. An essential requirement is that the interfacial tension between the oil and water phases γ, is reduced to a very low value by the interfacial film, giving a small but positive free-energy value. The dispersion of the droplets in the continuous phase increases the entropy of the system. Microemulsions form because the negative free energy changes due to the entropy of the dispersion of droplets in the continuous phase overcomes the positive product of the small interfacial tension and the large interfacial area A.

The curvature of the oil–water interface in microemulsions varies from highly curved towards oil (o/w) or water (w/o) to zero mean curvature in bicontinuous structures. The type of microemulsion that forms depends on the properties of the surfactant, cosurfactant and the oil. Although there are no strict rules for choosing the appropriate microemulsion components, there are a number of general guidelines based on empirical observations. The surfactant(s) chosen for a particular oil must:

1. lower interfacial tension to a very low value to aid dispersion processes during the preparation of the microemulsion.
2. be of the appropriate hydrophile-lipophile character to provide the correct curvature at the interfacial region for the desired microemulsion type, o/w, w/o or bicontinuous.
3. provide a flexible film that can readily deform round small droplets.

The analysis of film curvature for surfactant associations leading to microemulsion formation has been rationalized by Mitchell and Ninham. They used a packing ratio P defined as V/al, where V is the partial molar volume of the surfactant, a the cross sectional area (i.e. size) of the surfactant head group, and l the maximum length of the surfactant chain (46). The packing ratio provides a direct measure of HLB and is influenced by the same factors. Oil-in-water microemulsions are favored if the effective polar part of the surfactant is more bulky than the hydrophobic part, that is, P varies from 0 to 1, and the interface curves spontaneously towards water (positive curvature). Water-in-oil microemulsions form when the interface curves in the opposite direction, that is, P is greater than 1 (negative curvature). At zero curvature, when the HLB is balanced and P is zero, either bicontinuous or lamellar structures may form according to the rigidity of the film. The critical packing parameter P is based purely on geometric considerations. Hydration of the surfactant head group and penetration of the oil and the cosurfactant into the surfactant film also affect the packing and curvature, as summarized in Table 5, which also illustrates how formulation variables may be manipulated to produce a microemulsion of the desired type (47).

Most single-chain surfactants do not lower the oil–water interfacial tension sufficiently to form microemulsions nor are they of the correct molecular structure, and

Table 5 Factors affecting spontaneous curvature of monolayers

Variable	Curvature effect	Cause
Increase oil chain length	More positive	Less penetration of surfactant tail region
Addition of shorter chain cosurfactant	More positive	Alcohol swells head region more than tail region
Addition of longer chain cosurfactant	More negative	Alcohol swells surfactant chain region more than head region
Addition of salt (ionic surfactant)	More negative	Screened repulsion between polar head groups
Addition of salt (nonionic surfactant)	More negative	Headgroup size reduced by dehydration
Branched or double chained surfactant	More negative	Increased tail group area
Reduced surfactant head group size	More negative	
Increased temperature (nonionic surfactant)	More negative	Headgroup size reduced by dehydration
Increased temperature (ionic surfactant)	More positive	Increased surfactant counter-ion dissociation

(Adapted from Ref. 47.)

short- to medium-chain length alcohols are necessary as cosurfactants. The cosurfactant also ensures that the interfacial film is flexible enough to deform readily around each droplet as their intercalation between the primary surfactant molecules decreases both the polar head group interactions and the hydrocarbon chain interactions. Medium-chain alcohols such as pentanol and hexanol have been used by many investigators as they are particularly effective cosurfactants. They are not, however, suitable for pharmaceuticals due to their high irritant potential. Double-chain surfactants such as anionic Aerosol-OT (bis-2-ethylhexyl sulfosuccinate) or cationic DDAB (didodecyldimethylammonium bromide), which have relatively small head groups and bulky hydrophobic portions, are already of the required HLB to form w/o microemulsions spontaneously without a cosurfactant. Unfortunately, these widely investigated surfactants are too toxic for general pharmaceutical or biotechnological applications. Double-chain phospholipids such as the phosphatidylcholines of lecithin are an obvious possibility. Although lecithin is too lipophilic to form microemulsions, pharmaceutically acceptable microemulsions have been prepared from double-chain phospholipids by using acceptable cosurfactants such as ethanol, propanol, or *n*-butanol with isopropyl myristate (48, 51). Self-emulsifying drug delivery systems are composed of triglyceride oils and surfactant mixtures that undergo spontaneous emulsification when mixed with water (52). This principle is used in the commercial product Sandimmune Neoral®, which forms a microemulsion in situ when diluted by gastric fluid.

Formulation and Preparation of Microemulsions

As microemulsions are thermodynamically stable, they can be prepared simply by blending oil, water, surfactant, and cosurfactant with mild agitation. Once the appropriate microemulsion components have been selected, quaternary phase diagrams or ternary pseudo-phase diagrams may be constructed to define the extent and nature of the microemulsion regions and the surrounding two- and three-phase domains. The microemulsion region can be identified and characterized using the range of light, neutron, and X-ray scattering and other techniques such as NMR and microscopy (45). Problems arise in interpretation of data in systems of high droplet volume fraction due to interdroplet interactions. The normal practice of investigating systems at relatively low concentrations and then extrapolating to zero concentration in order to eliminate interparticle interactions cannot be applied to microemulsions as it is not possible to dilute the systems without affecting their structure. Hard sphere models, such as those adapted from Percus and Yevick, have been successfully used to analyze scattering data from concentrated w/o microemulsions (53).

REFERENCES

1. International Union of Pure and Applied Chemistry, IUPAC. *Manual of Colloid and Surface Chemistry*; Butterworths: London, 1971.
2. Garti, N.; Aserin, A. Double Emulsions Stabilized by Macromolecular Surfactants. *Micelles Microemulsions and Monolayers*; Shah, D.O. Ed.; Marcel Dekker, Inc.: New York, 1998; 333–362.
3. Davis, S.S.; Washington, C.; West, P.; Illum, L.; Liversidge, G.; Sternson, L.; Kirsh, R. Lipid Emulsions as Drug Delivery Systems. Ann. N. Y. Acad. Sci. **1987**, *507*, 75–88.
4. Eccleston, G.M.; Emulsions. *Encyclopedia of Pharmaceutical Technology*, 1st Ed.; Swarbrick, J., Boylan, J.C. Eds.; Marcel Dekker, Inc.: New York, 1992; 5, 137–188.
5. Block, L.H. Pharmaceutical Emulsions and Microemulsions. *Pharmaceutical Dosage Forms: Disperse Systems*; Lieberman, H.A., Rieger, M.M., Banker, G.S, Eds.; Marcel Dekker, Inc.: New York, 1996; 2, 47–109.
6. Rosoff, M.; Specialised Pharmaceutical Emulsions. *Pharmaceutical Dosage Forms: Disperse Systems*; Lieberman, H.A., Rieger, M.M., Banker, G.S., Eds.; Marcel Dekker, Inc.: New York, 1997; 3, 1–22.
7. Barry, B.W. *Dermatological Formulation. Percutaneous Absorption*; Marcel Dekker, Inc.: New York, 1983; 480.
8. Flynn, G.L.; Cutaneous and Transdermal Delivery: Processes and Systems of Delivery. *Modern Pharmaceutics*, 3rd Ed.; Banker, G.S., Rhodes, C.T. Eds.; Marcel Dekker, Inc.: New York, 1996; 239–298.
9. Eccleston, G.M.; The Microstructure of Semisolid Creams. Pharm. Int. **1986**, *7* (3), 63–70.
10. Eccleston, G.M.; Functions of Mixed Emulsifiers and Emulsifying Waxes in Dermatological Lotions and Creams. Colloids and Surfaces **1997**, 169–182.
11. Amselem, S.; Friedman, D.; Submicron Emulsions as Drug Carriers for Topical Administration. *Submicron Emulsions in Drug Delivery*; Benita, S. Ed.; Harwood Academic: Amsterdam, 1998; 9, 152–173.
12. Carrigan, P.; Bates, T.; Biopharmaceutics of Drug Administered in Lipid-Containing Dosage Forms 1: GI Absorption of Griseofulvin from an Oil-in-Water Emulsion in Rat. J. Pharm. Sci. **1973**, *62*, 1476–1414.
13. Collins Gold, L.C.; Lyons, R.T.; Bartholow, L.C.; Parenteral Emulsions for Drug Delivery. Adv. Drug Del. Rev. **1990**, *5*, 189–208.
14. Prankerd, R.J.; Stella, V.J.; The Use of Oil-In-Water Emulsions as a Vehicle for Parenteral Administration. J. Parent. Sci. Technol. **1990**, *44*, 139–149.
15. Floyd, A.G.; Jain, S. Injectable Emulsions and Suspensions. *Pharmaceutical Dosage Forms: Disperse Systems*; Lieberman, H.A., Rieger, M.M., Banker, G.S., Eds.; Marcel Dekker, Inc.: New York, 1996; 2, 261–318.

16. Nomura, T.; Koreeda, N.; Yamashita, F.; Takakura, Y.; Hashida, M. Effect of Particle Size on the Disposition of Lipid Carriers after Intratumoral Injection into Tissue Isolated Tumors. Pharm. Res. **1998**, *15* (1), 128–132.
17. Omotosho, J.A.; Whateley, T.L.; Florence, A.T. Release of 5-Fluorouracil from Intramuscular W/O/W Multiple Emulsions. Biopharm. and Drug Disposit **1989**, *10*, 257–268.
18. Von Dardel, O.; Mebius, C.; Mossberg, T.; Svensson, B. Fat Emulsion as a Vehicle for Diazepam. A Study of 9492 Patients. Br. J. Anaesth. **1983**, *55*, 41–47.
19. Lovell, M.W.; Johnson, H.W.; Hui, H.W.; Cannon, J.B.; Gupta, P.K.; Hsu, C.C. Less Painful Emulsion Formulations for Intravenous Administration of Clarithromycin. Int. J. Pharm. **1994**, *109*, 45–57.
20. Kirsh, R.; Goldstein, R.; Tarloff, J.; Parris, D.; Hook, J.; Hanna, N.; Bugelski, P.; Poste, G.J. An Emulsion Formulation of Amphoteracin B Improves the Therapeutic Index when Treating Systemic Murine Candidiasis. Infect. Dise. **1988**, *158*, 1065–1070.
21. Submicron Emulsions in Drug Targeting and Delivery. *Drug Targeting and Delivery*; Benita, S., Ed.; Harwood Academic: Amsterdam, 1998; 333.
22. Spahn, D.R. Current Status Of Artificial Oxygen Carriers. Adv. Drug Del. Rev. **2000**, *40*, 143–151.
23. Naveh, N.; Muchtar, S.; Benita, S. Pilocarpine Incorporated into a Submicron Emulsion Vehicle Causes Unexpectedly Prolonged Ocular Hypotensive Effects in Rabbits. J. Ocular Pharmacol. **1994**, *10* (3), 509–520.
24. Kararli, T.T.; Needham, T.E.; Schoenhard, G.; Baron, D.A.; Schmidt, R.E.; Katz, B.; Belonio, B. Enhancement of Nasal Delivery of a Renin Inhibitor in the Rat Using Emulsion Formulations. Pharm. Res. **1992**, *9*, 1024–1028.
25. Aikawa, K.; Matsumoto, K.; Uda, H.; Tanaka, S.; Shimamura, H.; Aramaki, Y.; Ysuchiya, S. Prolonged Release of Drug from O/W Emulsion and Residence in Rat Nasal Cavity. Pharm. Dev. Technol. **1998**, *3* (4), 461–469.
26. Mitra, R.; Pezron, I.; Chu, W.A.; Mitra, A.K. Lipid Emulsions as Vehicles for Enhanced Nasal Delivery of Insulin. Int. J. Pharm. **2000**, *205* (1–2), 127–134.
27. Mascioli, E.A.; Babayan, V.K.; Bistrian, B.R.; Blackburn, G.L. Novel Triglycerides for Special Medical Purposes. J. Parent. Ent. Nut. **1989**, *12* (6), 127S–132S.
28. Hedeman, H.; Brondsted, H.; Mullertz, A.; Frokjaer, S. Fat Emulsions Based on Structured Lipids (1,3 Specific Triglycerides): An Investigation of the In Vivo Fate. Pharm. Res. **1996**, *13* (5), 725–733.
29. Eccleston, G.M. Multiple-Phase Oil-in-Water Emulsions. J. Soc. Cosmet. Chem. **1990**, *41*, 1–22.
30. Nishikawa, M.; Yoshinobu, T.; Hashida, M. Biofate of Fat Emulsions. *Submicron Emulsions in Drug Targeting and Delivery*; Benita, S., Ed.; Harwood Academic: Amsterdam, 1998; 99–118.
31. Eccleston, G.M.; Florence, A.T. Application of Emulsion Theory to Complex and Real Systems. Int. J. Cosmet. Sci. **1985**, *7*, 195–212.
32. Hough, D.B.; Thompson, L. Effect of Nonionic Surfactants on the Stability of Dispersions. *Nonionic Surfactants. Physical Chemistry*; Schick, M.J., Ed.; Marcel Dekker, Inc.: New York, 1987; 601–676.
33. Washington, C. The Electrokinetic Properties of Phospholipid Stabilized Fat Emulsions. III. Interdroplet Potentials and Stability Ratios in Monovalent Electrolytes. Int. J. Pharm. **1990**, *64*, 67–73.
34. Rydhag, L.; Wilton, I. The Function of Phospholipids of Soybean Lecithin in Emulsions. Am. J. Oil Col. Chem. **1981**, *58*, 830–837.
35. Eccleston, G.M.; Behan-Martin, M.K.; Jones, G.R.; Townes-Andrews, E. Synchrotron X-Ray Investigations into the Lamellar Gel Phase Formed in Pharmaceutical Creams Prepared with Cetrimide and Fatty Alcohols. Int. J. Pharm. **2000**, *203*, 127–139.
36. Buscall, R.; Davis, S.S.; Potts, D.C. The Effect of Long-Chain Alkenes on the Stability of Oil-in-Water Emulsions. The Significance of Ostwald Ripening. Colloid Polym. Sci. **1979**, *257*, 636–644.
37. Davis, S.S.; Round, H.P.; Purewal, T.S. Ostwald Ripening and the Stability of Emulsion Systems: An Explanation for the Effect of an Added Third Component. J. Colloid Int. Sci. **1981**, *80* (2), 508–511.
38. Welin-Berger, K.; Bergenstahl, B. Inhibition of Ostwald Ripening in Local Anaesthetic Emulsions by Using Hydrophobic Excipients in the Disperse Phase. Int. J. Pharm. **2000**, *200* (2), 249–260.
39. Becher, P. Hydrophile-Lipophile Balance: An Updated Biography. *Encyclopedia of Emulsion Technology*; Becher, P., Ed.; Marcel Dekker, Inc.: New York, 1985; 2, 425–512.
40. Shinoda, K.; Saito, H. The Stability of O/W Type Emulsions as Functions of Temperature and the HLB of Emulsifiers: The Emulsification by PIT Method. J. Colloid Int. Sci. **1969**, *30*, 258–263.
41. Eccleston, G.M. Microemulsions. *Encyclopedia of Pharmaceutical Technology*, 1st Ed.; Swarbrick, J., Boylan, J.C., Eds.; Marcel Dekker, Inc.: New York, 1995; 9, 375–421.
42. Ritschel, W. Microemulsions for Improved Peptide Absorption from the Gastrointestinal Tract. Meth. Find. Exp. Clin. Pharmacol. **1991**, *13*, 205–220.
43. Constantinides, P.P.; Scalart, J.; Lancaster, C.; Marcello, J.; Marks, G.; Ellens, H.; Smith, P.L. Formulation and Intestinal Absorption Enhancement Evaluation of Water-In-Oil Microemulsions Incorporating Medium Chain Triglycerides. Pharm. Res. **1994**, *11* (10), 1385–1390.
44. Linn, E.E.; Pohland, R.C.; Byrd, T.K. Microemulsions for Intradermal Delivery of Cetyl Alcohol and Octyl Dimethyl PABA. Drug Dev. Ind. Pharm. **1990**, *16* (9), 899–920.
45. Attwood, D. Microemulsions. *Colloidal Drug Delivery Systems*; Kreuter, J., Ed.; Marcel Dekker, Inc.: New York, 1994; 66, 31–71.
46. Mitchell, D.J.; Ninham, B. Micelles Vesicles and Microemulsions. J. Chem Soc. Faraday Trans. **1981**, *2* (677), 601–629.
47. Fletcher, D.I.; Parrott, D. Protein Partitioning between Microemulsion Phases and Conjugate Aqueous Phases. *Structure and Reactivity in Reverse Micelles*; Pileni, M.P., Ed.; Elsevier: New York, 1988; 303–322.
48. Attwood, D.; Mallon, C.; Taylor, C.J. Phase Studies on Oil-in-Water Phospholipid Microemulsions. Int. J. Pharm. **1992**, *84*, R5–R8.
49. Aboofazeli, R.; Lawrence, M.J. Investigations into the Formation and Characterisation of Phospholipid Microemulsions. 1. Pseudo-ternary Phase Diagrams of Systems Containing Water-Lecithin-Alcohol-Isopropyl Myristate. Int. J. Pharm. **1993**, *93*, 161–175.

50. Aboofazeli, R.; Lawrence, M.J. Investigations into the Formation and Characterisation of Phospholipid Microemulsions. II. Pseudo-Ternary Phase Diagrams of Systems Containing Water-Lecithin-Isopropyl Myristate-Alcohol: Influence of Purity. Int. J. Pharm. **1994**, *106* , 51–61.
51. Aboofazeli, R.; Lawrence, M.J. Investigations into the Formation and Characterisation of Phospholipid Microemulsions. II. Pseudo-Ternary Phase Diagrams of Systems Containing Water-Lecithin-Isopropyl Myristate. Int. J. Pharm. **1994**, *111*, 63–72.
52. Pouton, C. Lipid Formulations for Oral Administration of Drugs: Non-Emulsifying, Self-Emulsifying and Self-Microemulsifying Drug Delivery Systems. Eur. J. Pharm. Sci. **2000**, *1* (11), S93–S98.
53. Percus, J.K.; Yevick, G.J. Analysis of Classical Statistical Mechanics by Means of Collective Co-ordinates. Phys. Rev. **1958**, *110*, 1–13.